REMARKS

In compete response to the Official Action dated September 5, 2001, applicants hereby elect with traverse a method for treatment of cancer for examination in the instant application. Applicants reserve the right to pursue claims directed to additional disease states in divisional application(s).

In addition, the independent claims do not recite a required combination of agents. The "invention" as claimed is not "an enhanced combination of harringtonines and another antitumor agent," as asserted in the Official Action. Instead, the invention as claimed relates to a method of treating cancer comprising administering via a subcutaneous mode of administration a harringtonine as recited in the claims. Claim 1 as filed included an additional agent as an *optional* ingredient. This is made more clear by deleting this language from claim 1 and reciting the presence of additional agents in dependent claims. Since a search for a method as claimed using a harringtonine will include a search for the harringtonine alone or in combination with other agents, these claims are properly included in this application. Since the additional agent is not mandatory in the claims, an election of an additional antitumor agent is not necessary.

The claims have also been amended to delete multiple dependencies and to make the claims more clear. These amendments do not narrow the scope of the claims. Additional claims have been added, and find support in original claims 1-10.

In addition, typographical errors in the formulas have been corrected. More specifically, the harringtonine formula (1) on page 2, about line 10, (2) in claim 1, page 19, about line 13, (3) in claim 3, page 21, about line 4, and (4) in the abstract, have been amended

to recite "$COZR^8$." That this was a typographical error would be clear to a person skilled in the art since "R^6" is never defined in the specification and "R^8" is defined but does not appear in the chemical formula. In addition, harringtonines are known compounds. In addition, on page 3, line 17, the recitation of "$Z\text{-}R^5$ is $NR^{12}R^{13}$, R^{12} and R^{13}" has been amended to recite "$Z\text{-}R^8$ is $NR^{12}R^{13}$, R^{12} and R^{13}." Support for this amendment may be found at the very least in claim 1, page 20, line 1.

No new matter has thus been added by these amendments.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney at (508) 339-3684.

Further and favorable action in the form of a notice of allowance is respectfully requested.

Respectfully submitted,

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Date: January 7, 2002

Attachment to Amendment and Response to Restriction Requirement dated January 7, 2002

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Page 2, Paragraph Beginning at Line 1

SCHEME 1: DEFINITION NOMENCLATURE AND NUMBERING OF CEPHALOTAXANES

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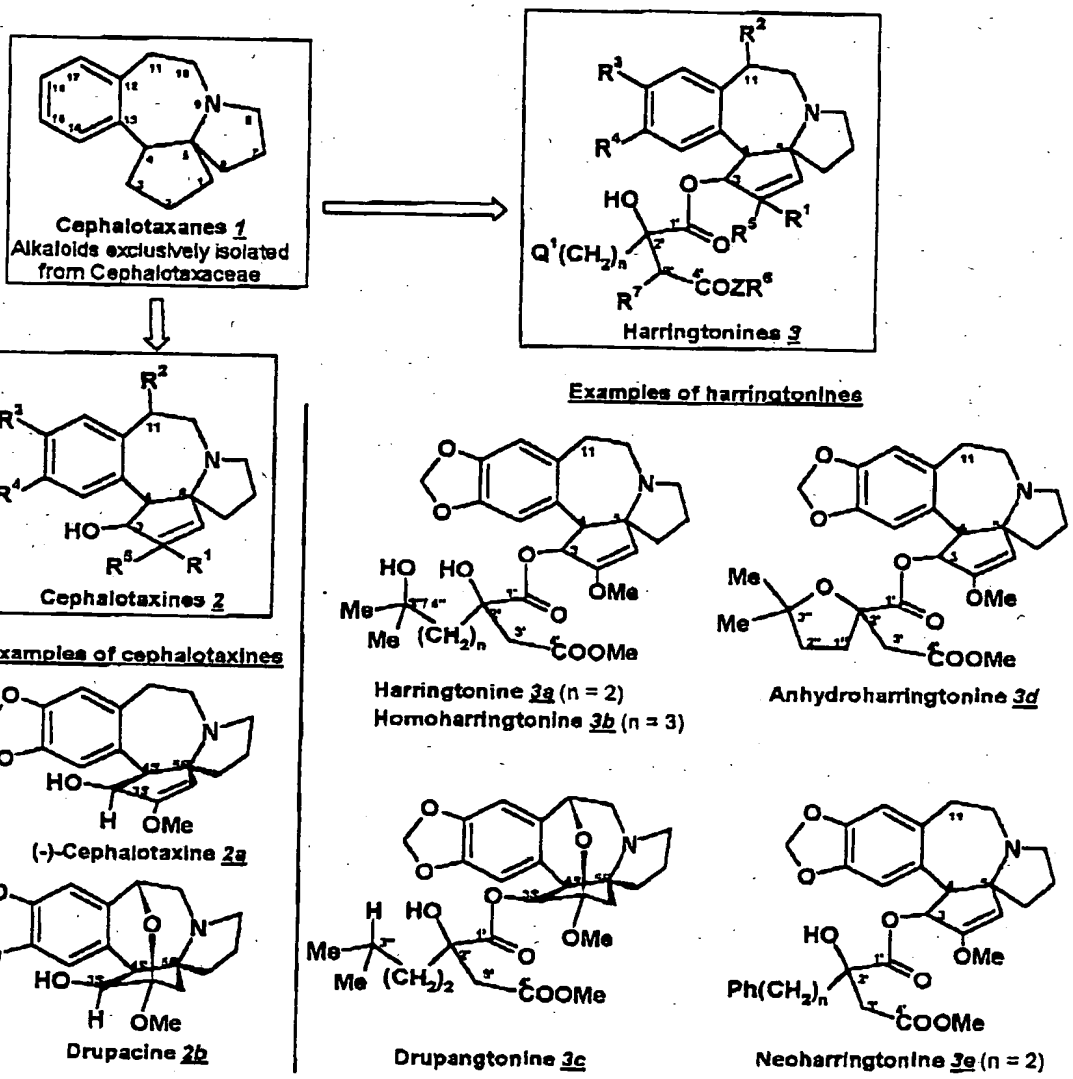

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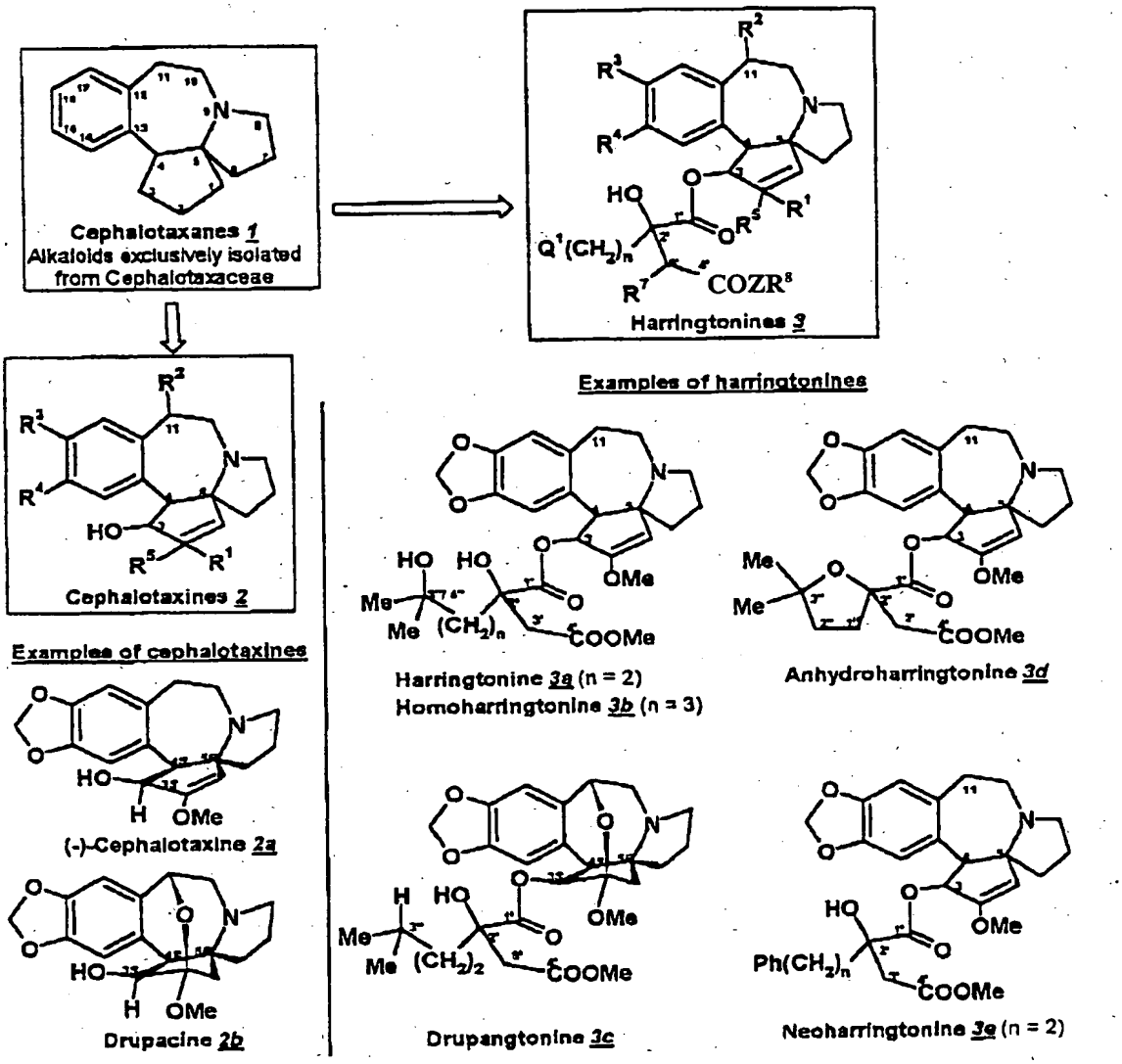

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Page 3, Paragraph Beginning at Line 1

In the above formulae 3 and 3 the different [substituants] substituents have the following definitions:

- R^1 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or null and

  R^2 is H or OH, or R^1, R^2 form together -O-,

  R^3 = R^4 = OMe or R^3 and R^4 form together -OCH_2O-,

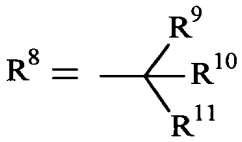
[•]

- n is 0 to 8,

[•]

- R^5 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or O-aryl,

  Z = O, S, or NH, and



  or [Z-R^5] Z-R^8 is $NR^{12}R^{13}$, R^{12} and R^{13} representing respectively R^9 and R^{10},

  R^9, R^{10}, R^{11} are independently H, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl, C_2-C_{30} alkynyl, C_1-C_{30} trihalogenoalkyl, C_1-C_{30}

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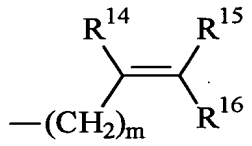
alkylamino-(C_1-C_{30})alkyl, C_1-C_{30} dialkylamino(C_1-C_{30})-alkyl, or amino-(C_1-C_{30})-alkyl, or



where R^{14}, R^{15}, R^{16} are independently H, halogen, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl, [or] C_2-C_{30} alkynyl, or C_1-C_{30} trihalogenoalkyl, and m is 0 to 4,

- each of these groups optionally including [or not] heteroatom(s).

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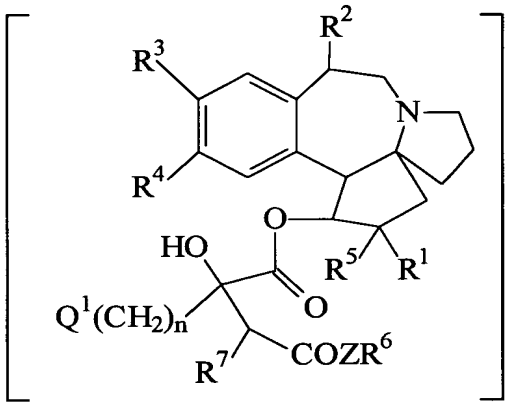
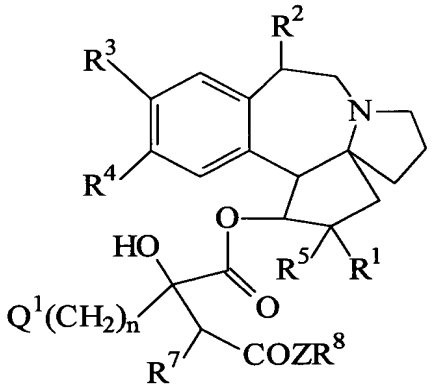
Marked-up Claims 1-2 and 4-10

1. (Amended) A [new] method of [therapy] treating cancer comprising administering to a patient in need of such treatment using [the] a subcutaneous mode of administration [of formulations based upon harringtonines] a harringtonine [including their salts tautomeric forms] having the formula





[where] wherein:

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Marked-up Claims 1-2 and 4-10

- R^1 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or null and

  R^2 is H or OH, or R^1, R^2 form together -O-,

  R^3 = R^4 = OMe or R^3 and R^4 form together -OCH_2O-,

[•]

- n is 0 to 8,

[•]

- R^5 is H, OH, OMe, O-(C_1-C_{30})-alkyl, O-aryl-(C_1-C_{30})-alkyl, O-(C_2-C_{30})-alkenyl, O-(C_3-C_{30})-cycloalkyl or O-aryl,

  Z = O, S, or NH, and

$$R^8 = \begin{array}{l} R^9 \\ \diagup \\ -\!\!<\!\!- R^{10} \\ \diagdown \\ R^{11} \end{array}$$

or Z-R^8 is $NR^{12}R^{13}$, R^{12} and R^{13} representing respectively R^9 and R^{10},

R^9, R^{10}, R^{11} are independently H, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl, C_2-C_{30} alkynyl, C_1-C_{30} trihalogenoalkyl, C_1-C_{30} alkylamino-(C_1-C_{30})alkyl, C_1-C_{30} dialkylamino(C_1-C_{30})-alkyl, [or] amino-(C_1-C_{30})-alkyl, or

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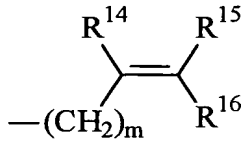
Marked-up Claims 1-2 and 4-10



where R^{14}, R^{15}, R^{16} are independently H, halogen, C_1-C_{30} alkyl, C_3-C_{30} cycloalkyl, aryl, aryl-(C_1-C_{30})-alkyl, C_2-C_{30} alkenyl, [or] C_2-C_{30} alkynyl, or C_1-C_{30} trihalogenoalkyl, and m is 0 to 4,

each of these groups optionally including [or not] heteroatom(s),

or salt or tautomeric form thereof [their combination with another antitumor agent or a mixture of antitumor agents useful for the treatment of a disease in humans or animals, particularly cancers, leukemias, lymphomas, parasite diseases or chemotherapeutic resistance to other agents, in using a formulation specifically adapted for subcutaneous administration].

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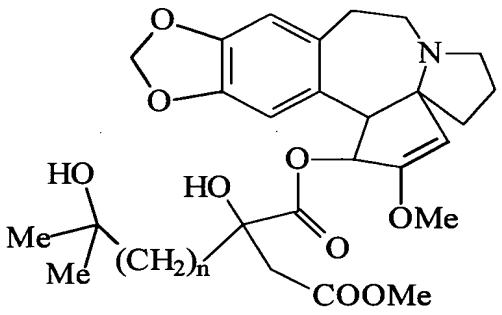
Marked-up Claims 1-2 and 4-10

2. (Amended) The method of claim 1 [to 2] where the harringtonine is homoharringtonine or harringtonine having the following formula



where n = 1 or 2.

4. (Amended) The method of [claims 1 to 3] claim 15 in which the acid which forms a salt of harringtonines is [hydrochlorid] hydrochloric acid or tartaric acid.

5. (Amended) The method of [therapy of claims 1 to 4] claim 1 in which the harringtonines are solutions or hydrophilic freeze-dried powder ready-to-constitute of buffered salt of homoharringtonine or harringtonine of which the level of chromatographic purity suitable for medical use is higher than 99.7%.

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Marked-up Claims 1-2 and 4-10

6. (Amended) The method of [therapy of claims 3 to 5] claim 15 in which the pH of the formulation or constituted solution for injection is [included] between 5.5 and 8.

7. (Amended) The method of [therapy of claims 1 to 6] claim 1 in which harringtonines are combined with another pharmaceutically acceptable agent in the same injection.

8. (Amended) The method of [therapy of] claim 7 in which the [other] additional agent is a nucleoside[, preferably cytosine arabinoside].

9. (Amended) The method of therapy of [claims 1 to 8] claim 1 in which the subcutaneous mode of administration is performed by bolus injection at regular intervals [such as one to four injection a day during 1 to n days for a cycle of n days, n being preferably 28].

10. (Amended) The method of [therapy of claims 1 to 8] claim 1 in which the subcutaneous mode of administration is performed by continuous subcutaneous infusion.